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● INVITED REVIEW

# Mitochondrial quality control in amyotrophic lateral sclerosis: towards a common pathway?

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## Abstract

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder characterized by loss of upper and lower motor neurons. Different mechanisms contribute to the disease initiation and progression, including mitochondrial dysfunction which has been proposed to be a central determinant in ALS pathogenesis. Indeed, while mitochondrial defects have been mainly described in ALS-linked SOD1 mutants, it is now well established that mitochondria become also dysfunctional in other ALS conditions. In such context, the mitochondrial quality control system allows to restore normal functioning of mitochondria and to prevent cell death, by both eliminating and replacing damaged mitochondrial components or by degrading the entire organelle through mitophagy. Recent evidence shows that ALS-related genes interfere with the mitochondrial quality control system. This review highlights how ineffective mitochondrial quality control may render motor neurons defenseless towards the accumulating mitochondrial damage in ALS.

**Key Words:** *C9orf72*; *FUS*; *SOD1*; *Optineurin*; *Parkin*; *PGC-1α*; *PINK1*; *TDP-43* proteinopathies; *TBKI*; *VCP*

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## Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by a progressive degeneration of motor neurons in the spinal cord, brain stem and cerebral cortex. An important histopathological hallmark of ALS is the presence of cytosolic protein aggregates in motor neurons and surrounding glia. Patients develop muscle weakness, progressive paralysis and spasticity. Cognitive defects are rare whereas 20% of ALS cases also show frontotemporal dementia. Over time, complications appear with eating difficulties (dysphagia) and respiratory distress (orthopnea and dyspnea). The survival time from diagnosis is 2–5 years. Among treatments, riluzole prolongs life by only a few months but without ameliorating motor functions (Miller et al., 2012) and the antioxidant edavarone has recently been approved by the Federal Drug Administration for ALS.

Most ALS cases (90%) are sporadic with no family history and the remaining 10% are inherited forms, indicating that both environmental and genetic factors are involved in the disease etiology. Because mutations in the *copper/zinc superoxide dismutase 1 (SOD1)* gene were discovered first in 1993 (Rosen et al., 1993), significant advances in ALS pathogenesis come from animal models expressing mutant forms of SOD1. In the last decade, an important breakthrough was achieved with the identification of new ALS-linked genes. Among these, mutations in two DNA/RNA binding proteins: *TAR DNA-binding protein of 43 kDa (TDP-43)* and *fused in sarcoma (FUS)* have put RNA metabolism as a key mechanism in ALS (Sreedharan et al., 2008; Kwiatkowski et al., 2009; Vance et al., 2009). Non-mutated TDP-43 has also been detected in aggregates of the majority of ALS patients, suggesting that deregulation and mislocalization of

wild-type TDP-43 mediate both sporadic and familial ALS (Arai et al., 2006). More recently, an abnormal expansion of hexanucleotide (GGGGCC) repeat in a non-coding region of the *chromosome 9 open reading frame 72 gene (C9orf72)* was identified as the most common cause of familial ALS (40–50%) (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Despite the lack of an ATG start codon, the hexanucleotide repeat expansion is translated into dipeptide repeat proteins (Ash et al., 2013). As a possible mechanism, sequestration of RNA-binding proteins by expanded repeat RNA may synergistically contribute to the toxicity along with the accumulation of dipeptide repeat proteins (Rohrer et al., 2015). Beyond RNA processing, components of protein/organelle quality control have emerged as important causal factors of ALS, including *p97/valosin-containing protein (VCP)*, *ubiquilin*, *optineurin* and *p62/SQSTM1*. As a consequence, many cellular processes are affected including abnormal protein aggregations, excitotoxicity, mitochondrial abnormalities, oxidative damage and inflammation. One important challenge in the future will be to determine which among these mechanisms are crucial and common in ALS pathogenesis. This may definitely help to identify relevant therapeutic targets. In this review, we discuss the latest evidence showing that compromised mitochondrial quality control is a common determinant in ALS.

## Mitochondrial Quality Control Pathways

The major function of mitochondria is the production of adenosine triphosphate (ATP) through the oxidative phosphorylation system (OXPHOS). During cell respiration, electrons are transferred to oxygen molecules and produce superoxide anions. Because they are highly toxic, superoxide anions are usually neutralized by antioxidant enzymes. How-

ever in pathological conditions, mitochondrial dysfunction leads to ATP depletion, superoxide anion overload and release of proapoptotic molecules such as cytochrome c. Cells have nevertheless adapted a mitochondrial quality control (MQC) system to overcome mitochondrial defects. MQC is particularly crucial for neurons which are long living cells and thereby can accumulate damage in mitochondria.

### Mitochondrial protein quality control

Quality control of mitochondrial proteins restores the native conformation and function of damaged mitochondrial proteins, or eliminates them if they reach a point of no return. This system therefore assures protein homeostasis in mitochondria, *via* the ubiquitin-proteasome (UPS) system and mitochondrial chaperones and proteases.

The UPS selectively eliminates proteins of the outer mitochondrial membrane (OMM) by tagging them with lysine 48-linked polyubiquitin chain (K48 chain). Proteins with K48 chains are extracted by the segregase p97/VCP, then delivered to the proteasome for degradation (Tanaka et al., 2010). Strikingly, some studies have suggested that damaged proteins localized at the inner mitochondrial membrane (IMM) or in the mitochondrial matrix can be retrotranslocated to the OMM where they will be ubiquitinated and eliminated by the UPS (Margineantu et al., 2007; Azzu and Brand, 2010).

Heat-shock proteins (Hsp), especially Hsp60 and Hsp70 are known for their role in importing newly synthesized mitochondrial proteins into mitochondrial matrix and conferring their native conformation (Ostermann et al., 1989; Voos et al., 1996; Liu et al., 2001). When exposed to stress, Hsp also stabilize damaged mitochondrial proteins, preventing them from aggregating (Bender et al., 2011). If proteins are highly damaged and become irreparable, then Hsp70 maintains them in a soluble state until they are proteolyzed by mitochondrial proteases (Wagner et al., 1994).

Misfolded mitochondrial proteins which are unable to recover their native form are redirected to the mitochondrial proteolytic system. Proteases Lon and AAA<sup>+</sup>/FtsH (Filament-forming temperature sensitive) degrade aberrant proteins in the mitochondrial matrix and IMM, respectively. Lon has both chaperone and proteolytic activities and is considered as the main mitochondrial protease, since Lon deletion in yeast results in an increased number of mitochondrial protein aggregates (Bender et al., 2011). Lon mainly targets mitochondrial enzymes with Fe-S clusters which become easily unstable after covalent oxidative modification (Bota and Davies, 2002; Bender et al., 2011). In contrast, AAA<sup>+</sup> proteases do not focus on specific proteins but degrade all sorts of misfolded proteins in the IMM (Leonhard et al., 1999), as well as non-assembled proteins such as subunits of respiratory complexes (Arlt et al., 1998).

### Mitochondrial biogenesis

Mitochondrial biogenesis, or mitochondriogenesis, is the process by which new mitochondrial components are synthesized to replenish damaged mitochondria. This mechanism also allows the genesis of proteins involved in OXPHOS and in other crucial mitochondrial functions. Activating mitochondriogenesis within cells is beneficial during

mitochondrial dysfunction since it preserves mitochondrial energy metabolism and integrity and therefore prevents cell death and pathology occurrence.

Mitochondriogenesis is regulated by the master transcriptional coactivator peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) coactivator-1 $\alpha$  (PGC-1 $\alpha$ ). PGC-1 $\alpha$  coordinates the expression of mitochondrial components between the nuclear and mitochondrial genomes, through its binding to nuclear receptors (PPAR- $\gamma$ , estrogen-related receptor  $\alpha$ ) or transcription factors such as nuclear respiratory factors (NRFs) (Puigserver and Spiegelman, 2003). Moreover, PGC-1 $\alpha$  increases the expression levels of NRFs (Wu et al., 1999). Then, NRFs regulate the expression of respiratory complex subunits (Wu et al., 1999), as well as proteins implicated in mitochondrial import (Blesa et al., 2007) and heme biosynthesis (Braidotti et al., 1993). NRFs also modulate the expression of mitochondrial transcription factor A (TFAM) which is responsible for mitochondrial DNA transcription and replication (Virbasius and Scarpulla, 1994). PGC-1 $\beta$  and PGC-1 related coactivator, both members of the PGC-1 $\alpha$  co-activator family, also contribute to mitochondrial biogenesis (Lin et al., 2003; Gleyzer et al., 2005), but their role has not been fully elucidated yet.

Apart from PGC-1 $\alpha$ , silent mating type information regulation two-1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK) have been shown to contribute to mitochondrial biogenesis. SIRT1 is a NAD-dependent protein deacetylase which regulates the expression of genes involved in mitochondrial respiration through PGC-1 $\alpha$  (Lagouge et al., 2006). Indeed, SIRT1 directly interacts with PGC-1 $\alpha$  and activates it (Nemoto et al., 2005; Rodgers et al., 2005). Furthermore, the AMPK kinase is an energy cell sensor which interrupts ATP consumption and activates ATP-producing pathways during energy-demanding periods. In this case, AMPK induces mitochondrial biogenesis and activates PGC-1 $\alpha$  through direct phosphorylation (Jäger et al., 2007) or indirectly by stimulating SIRT1 (Cantó et al., 2009). Consequently, the AMPK/SIRT1/PGC-1 $\alpha$  axis plays a key role in maintaining the mitochondrial and cellular energy metabolism in stress conditions.

### Mitochondrial dynamics: fission versus fusion

Mitochondria form a highly dynamic network. Fission and fusion events control the shape, size and number of mitochondria and allow the exchange of proteins and lipids. The fission-fusion balance is necessary to regulate mitochondrial distribution during cell division and differentiation, but also to maintain mitochondrial integrity and cell survival during stress periods (Twig et al., 2008). Indeed, whereas fission facilitates segregation and elimination of defective mitochondria, fusion repairs the damaged mitochondrial DNA and mixes the content of both functional and defective mitochondria.

Mitochondrial fission is mainly regulated by the cytoplasmic protein, dynamin-related protein 1 (DRP1) (Smirnova et al., 2001). While still debated, DRP1 binding on mitochondria may require receptors on the OMM such as mitochondrial fission factor (Mff), Fission 1 (Fis1) and mitochondrial elongation factors (MIEF) (Palmer et al., 2011; Zhao et al., 2011a). Then, DRP1 oligomerizes and forms a constrictive

ring around the OMM (Smirnova et al., 2001). GTP hydrolysis by DRP1 triggers the mitochondrion fragmentation. Interestingly, mitochondria-associated membranes (MAMs) with endoplasmic reticulum (ER) facilitate DRP1 recruitment to the OMM and define the position of mitochondrial division sites (Friedman et al., 2011).

Mitochondrial fusion is an important mechanism of the MQC system, mostly because it permits the exchange of mitochondrial DNA and other constituents such as respiratory complexes between adjacent mitochondria to conserve their integrity (Legros et al., 2004). In addition, fusing intact and dysfunctional mitochondria together allows the “dilution” of local damaged components. Fusion between IMM and OMM occurs through distinct yet complementary mechanisms, *via* optic atrophy 1 (OPA1) and mitofusins (Mfns), respectively.

Long isoforms of OPA1 (L-OPA1) are subjected to proteolytic cleavage by intramitochondrial proteases, generating short isoforms called S-OPA1 (Song et al., 2007). It is proposed that L-OPA1 is anchored to the IMM whereas S-OPA1 is enriched in the intermembrane space (Satoh et al., 2003; Cipolat et al., 2006; Ishihara et al., 2006). L-OPA1 and S-OPA1 interact together to regulate IMM fusion (Song et al., 2007; Zick et al., 2009), although it was initially thought that only L-OPA1 is required for fusion (Ishihara et al., 2006; Anand et al., 2014). However, in stress conditions, reduced mitochondrial membrane potential ( $\Delta\psi_m$ ) promotes massive cleavage of L-OPA1 to S-OPA1, therefore altering the fusion process (Head et al., 2009). Of note, the presence of OPA1 on only one of the two adjacent mitochondria is sufficient to allow their fusion (Song et al., 2009).

OMM fusion is regulated by mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2). Mfns are characterized by very similar sequences (77% of similarity, 60% of identity) with a slight difference in the number of amino acids (741 amino acids for Mfn1 *versus* 757 amino acids for Mfn2) (Santel and Fuller, 2001). Mfn1 yet seems to be more indispensable for mitochondrial fusion than Mfn2 (Cipolat et al., 2004; Ishihara et al., 2004). At the structural level, Mfns essentially possess a GTPase domain, as well as two «coiled-coil» domains with heptad repeats (Rojo et al., 2002) which allow Mfns to interact with each other and form homo/heterodimers (Chen et al., 2003). Following GTP hydrolysis, Mfns change their conformation and force the outer membranes of adjacent mitochondria to fuse together (Chen et al., 2003). Interestingly, the absence of Mfns *in vitro* slows down the fusion of both outer and inner mitochondrial membranes, whereas OPA1 is dispensable for OMM fusion (Song et al., 2009). This indicates that Mfns are also required for IMM fusion. Apart from their fusogenic role, Mfns exert other mitochondrial functions. For instance, they promote mitochondrial transport by interacting with the mitochondrial membrane GTPase Miro and the kinesin adaptor Milton (Misko et al., 2010). Strikingly, Mfn2 is not exclusively mitochondrial; it is also present on ER surface where it interacts with mitochondrial Mfn2 to tether the two organelles. Accordingly, Mfn2 deficiency increases the distance between ER and mitochondria and alters the efficacy of calcium import from ER to mitochondria (De Brito and Scorrano, 2008).

### Mitochondrial-derived vesicles

A recently discovered mechanism involving structures called

mitochondrial-derived vesicles (MDV) has been shown to eliminate damaged mitochondrial components (for review, see Roberts et al., 2016). MDVs are small vesicles of 70 to 150 nm which contain damaged proteins and lipids originating from different compartments of mitochondria (Neuspiel et al., 2008). The generation of MDVs is considered as an early response of mitochondria to oxidative stress, since they appear in the first minutes after the stress-inducing agent has been applied (Soubannier et al., 2012a). Moreover, this process does not require neither a dissipation of the  $\Delta\psi_m$  nor the intervention of fission factor DRP1 (Neuspiel et al., 2008; Soubannier et al., 2012a; McLelland et al., 2014). Indeed, it has been shown that MDVs appear before the stress-induced mitochondrial fragmentation. *In vitro* experiments have established that the nature of the cargo in MDVs depends on the mitochondrial target of the stress. For instance, the application of antimycin A, an inhibitor of respiratory chain complex III, increases the formation of MDVs which are particularly enriched in oxidized complex III subunits (Soubannier et al., 2012b). Following their split from mitochondria, MDVs are sent to be degraded in lysosomes (Soubannier et al., 2012a; McLelland et al., 2014). They can also be transported to peroxisomes (Neuspiel et al., 2008), although the purpose of this mechanism is still unclear. The formation of MDVs would therefore constitute a first line of defense against total mitochondrial dysfunction. However in extreme conditions, and to insure its survival, cells are forced to entirely eliminate defective mitochondria through a process involving lysosomes but also, unlike MDVs, the autophagy machinery, so called mitophagy (Soubannier et al., 2012a; McLelland et al., 2014).

### Mitophagy

Mitophagy is a selective macroautophagy process during which irreparable mitochondria are degraded. It therefore prevents the accumulation of defective mitochondria and limits the release of reactive oxygen species and proapoptotic factors. During mitophagy, mitochondria are engulfed by a structure called phagophore, forming an autophagosome which then fuses with a lysosome before its content is degraded. As the other types of autophagy, mitophagy occurs in the perinuclear space of cells where lysosomes are particularly enriched. It is mainly orchestrated by the PINK1/Parkin pathway (Martinez-Vicente, 2017; Rüb et al., 2017; Whitworth and Pallanck, 2017). These genes have been largely studied in the context of Parkinson's disease. Indeed, mutations in *PINK1* (*PARK6*) and *parkin* (*PARK2*) genes contribute to familial forms of this disease (Kitada et al., 1998; Valente et al., 2004).

PTEN-induced kinase 1 (PINK1) is a mitochondrial serine/threonine kinase which in physiological conditions is cleaved by different intramitochondrial proteases (Gakh et al., 2002; Deas et al., 2011). However, following an abnormal dissipation of the  $\Delta\psi_m$ , PINK1 mitochondrial import and proteolysis are blocked. PINK1 therefore accumulates on the OMM and recruits its partner Parkin, a cytoplasmic E3 ubiquitin ligase (Matsuda et al., 2010; Narendra et al., 2010). The existence of a genetic epistasis between PINK1 and Parkin has been essentially highlighted in *Drosophila* (Ziviani et al., 2010). PINK1 phosphorylates Parkin, stimulating its ubiquitin ligase activity and its translocation to impaired mitochondria (Shiba-Fukushima et al., 2014). Lately, additional Parkin-re-

cruiting mechanisms have been brought to light. Indeed, it has been demonstrated that PINK1 is able to phosphorylate ubiquitin on serine 65 (S65), which then binds to Parkin, activates it and induces its translocation to mitochondria (Kane et al., 2014; Okatsu et al., 2015). This explains why Parkin is found polyubiquitinated during mitophagy (Geisler et al., 2010). Conversely, Parkin recruitment to mitochondria is inhibited when a non-phosphorylatable form of ubiquitin (ubiquitin S65A) is expressed. Moreover, Kazlauskaitė et al. (2015) and Koyano et al. (2014) have shown that, in addition of Parkin phosphorylation and activation by PINK1, its interaction with phospho-ubiquitins helps it gain a maximal level of activity. Ubiquitin is therefore considered as both an activator and a substrate of Parkin. Finally, proteins located on the OMM, such as Mfn2, can be phosphorylated by PINK1 and therefore serve as receptors to recruit Parkin to deficient mitochondria (Ziviani et al., 2010; Chen and Dorn, 2013). After its activation, Parkin ubiquitinates several proteins on the OMM mainly *via* K63 and K48 ubiquitin chains: K63 chains allow the recognition of damaged mitochondria by phagophores, whereas proteins tagged with K48 chains are degraded by the proteasome (Geisler et al., 2010; Chan et al., 2011).

The PINK1/Parkin pathway manages mitophagy through several mechanisms. Firstly, it induces the fragmentation of dysfunctional mitochondria, therefore segregating damaged mitochondria: daughter mitochondria with a weak  $\Delta\psi_m$  are eliminated, while those with a high  $\Delta\psi_m$  undergo fusion (Twig et al., 2008). Mitochondrial fragmentation during mitophagy is mainly triggered by Parkin-mediated ubiquitination and degradation of Mfns (Gegg et al., 2010; Ziviani et al., 2010). Secondly, PINK1 and Parkin immobilize defective mitochondria by degrading Miro which links mitochondria to microtubule motors (Kane and Youle, 2011). Thus, blocking movement of impaired mitochondria facilitates their engulfment by autophagic phagophores. Thirdly, the PINK1/Parkin pathway induces the formation and maturation of phagophores near dysfunctional mitochondria by recruiting autophagy initiators such as Unc51-Like Kinase 1 (ULK1) (Lazarou et al., 2015) and Beclin1 (Michiorri et al., 2010). Generated phagophores can then recognize Parkin-induced ubiquitinated mitochondria *via* cytoplasmic adaptor proteins, of which the most studied are Optineurin (Wong and Holzbaur, 2014; Heo et al., 2015) and p62/SQSTM1 (Geisler et al., 2010). Adaptors are structurally able to bind ubiquitinated OMM proteins *via* their ubiquitin-binding domain and the autophagosome-associated protein LC3 (microtubule-associated protein 1A/1B-Light Chain 3) *via* their LC3-interacting region domain. The binding of autophagosomes to adaptors depends on their phosphorylation by the kinase TANK-binding kinase 1 (TBK1), which is co-recruited along with her partner Optineurin (Matsumoto et al., 2015; Moore and Holzbaur, 2016). Once mitochondria-containing autophagosomes are formed and fused with lysosomes, their content is digested *via* lysosomal hydrolases. Interestingly, PINK1 and Parkin have been shown to induce the formation of lysosome-degraded MDVs before mitophagy activation (McLelland et al., 2014), indicating that the PINK1/Parkin pathway regulates mitochondrial integrity at different levels.

Finally, mitophagy can also occur through a PINK1/Parkin-independent manner. Novel autophagy receptors located in mitochondria and capable of direct interaction with LC3 have been identified, including Bcl-2 and adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) and Nix/BNIP3L (BNIP3-Like) (Novak et al., 2010; Rikka et al., 2011), or FUNDC1 (FUN14 domain-containing protein 1) (Liu et al., 2012). Apart from mitophagy receptors, cardiolipin redistribution in mitochondria turned out to be a potential mitophagy signal. When mitochondria become dysfunctional, cardiolipin is retrotranslocated from the IMM to the OMM where it recruits phagophores by associating with LC3 (Chu et al., 2013).

## Mitochondrial Quality Control Defects in ALS

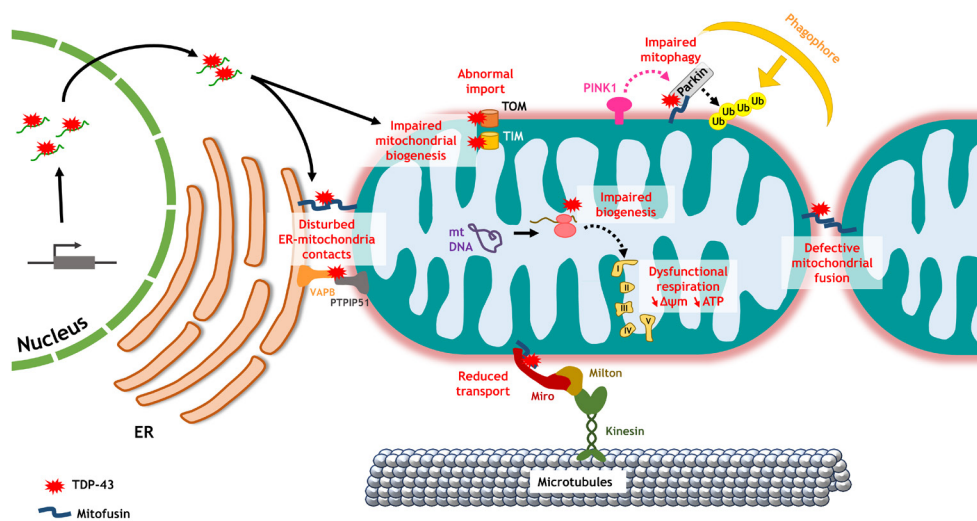
MQC defects in ALS have been previously reported in mutant SOD1 models (for reviews, see Shi et al., 2010; Palomo and Manfredi, 2015; Edens et al., 2016). Indeed, mutant SOD1 has an increased tendency to localize in mitochondria and leads to the accumulation of defective mitochondria. In this review, we mostly focus on new ALS genes with a particular interest in TDP-43 which is recognized as a major cause of the disease. MQC defects are summarized in **Additional Table 1**.

### Mitochondrial protein quality control in ALS

So far, the state of mitochondrial protein quality control in ALS has not been fully investigated. It has been demonstrated on mice spinal cord and *in vitro* neuronal models that ALS mutant SOD1 alters the expression of Hsp70 (Fukada et al., 2004; Yamashita et al., 2007) and downregulates the mitochondrial protease Lon (Fukada et al., 2004). On the other hand, TDP-43 and FUS abnormally interact with the mitochondrial chaperone Hsp60 in different ALS models (Freibaum et al., 2010; Deng et al., 2015), exacerbating mitochondrial dysfunction (Deng et al., 2015).

### Mitochondrial biogenesis in ALS

It is becoming increasingly evident that mitochondrial biogenesis is impaired in ALS. Current studies are aiming to find possible therapeutic targets to restore normal mitochondrial biogenesis and slow down the disease progression, and PGC-1 $\alpha$  seems to be a suitable candidate. Indeed, PGC-1 $\alpha$  and its downstream effector NRF1 are downregulated in spinal cord and muscles tissues of patients and mutant SOD1 mice (Thau et al., 2012; Russell et al., 2013). Interestingly, it has been shown that single-nucleotide polymorphisms reported in the brain-specific promoter region of PGC-1 $\alpha$  modify age of onset and survival of ALS patients and mutant SOD1 mice (Eschbach et al., 2013). So far, strategies aiming to increase PGC-1 $\alpha$  expression in ALS models were very fruitful. PGC-1 $\alpha$  overexpression protected against mitochondrial fragmentation and neuronal death in rat motor neurons expressing mutant SOD1 (Song et al., 2013). It also slowed the disease progression in mutant SOD1 mice by preserving their motor activity and attenuating motor neuron degeneration, even though the effect on survival is debated (Liang et al., 2011; Zhao et al., 2011b; Golko-Perez et al., 2017). PGC-1 $\alpha$  upregulation in mutant SOD1 mouse muscles also delays muscle atrophy but without affecting survival



**Figure 1 Mitochondrial quality control defects mediated by TDP-43 dysregulation.**

TDP-43 impairs biogenesis of mitochondrial proteins by altering nuclear-encoded or mitochondria-transcribed mRNA, or by preventing protein import to mitochondrial matrix through TOM/TIM translocases. In particular, TDP-43 perturbs the expression and assembly of complex I subunits leading to mitochondrial dysfunction, as well as mitofusin which causes excessive fragmentation of mitochondria. Mitofusin downregulation may also affect mitochondrial transport and mitophagy. TDP-43 disturbs ER-mitochondria contacts as well by blocking the interaction between VAPB and PTPIP51, and probably between both organelle's mitofusins.  $\Delta\psi_m$ : mitochondrial membrane potential; ER: endoplasmic reticulum; mt: mitochondrial; PINK1: PTEN-induced kinase 1; PTPIP51: protein tyrosine phosphatase interacting protein 51; TDP-43: TAR DNA-binding protein of 43 kDa; TIM: translocase of the inner membrane; TOM: translocase of the outer membrane; Ub: ubiquitin; VAPB: vesicle-associated membrane protein-associated protein B.

(Da Cruz et al., 2012). Furthermore, treating mutant SOD1 mice with PPAR- $\gamma$  agonist pioglitazone ameliorated their survival and motor performance and reduced motor neuron loss (Kiaei et al., 2005; Schutz, 2005).

The toxic effect of TDP-43 on mitochondrial biogenesis in ALS has been lately brought to light. AMPK activity was found drastically diminished in spinal cords and brains of transgenic mice carrying the A315T mutation (Perera et al., 2014). Transcriptome analyses performed on A315T mutant TDP-43 mice revealed a dysregulation of RNA regulating OXPHOS or other mitochondrial functions (Stribl et al., 2014). More recently, Wang et al. (2016) demonstrated a direct role of TDP-43 in mitochondrial biogenesis impairment using different cell models, including rat primary neurons and patient fibroblasts (Figure 1). In physiological conditions, wild-type TDP-43 is poorly localized at mitochondria. However, when it is overexpressed or carries ALS mutations, TDP-43 abundantly accumulates on the IMM. In this case, it binds to mitochondria-transcribed mRNA encoding for the complex I subunits ND3 and ND6 and blocks their protein translation (Wang et al., 2016). Therefore, TDP-43 specifically reduces complex I assembly and impairs ATP production (Wang et al., 2016). The same group also showed that TDP-43 abnormally interacts with translocases of the OMM, Tom20 and Tom70, or of the IMM, Tim77, altering the import of nuclear-encoded mitochondrial proteins (Wang et al., 2016) (Figure 1). We and others have demonstrated that TDP-43 also deregulates the expression of nuclear-encoded mitochondrial proteins such as Mfns in rat and fly brain neurons (Sephton et al., 2011; Khalil et al., 2017). TDP-43 therefore perturbs the expression of mitochondrial proteins encoded by both nuclear and mitochondrial genomes. Thus increasing mitochondrial biogenesis is expected to counteract TDP-43-induced toxicity. Accordingly, PPAR- $\gamma$  agonist pioglitazone rescues locomotor

defects in *Drosophila* expressing TDP-43 in motor neurons (Joardar et al., 2015).

On the other hand, decreased levels of PGC-1 $\alpha$  have been reported in mice expressing mutant FUS in brain stem and spinal cord (Bayer et al., 2017), and application of PPAR- $\gamma$  agonist rosiglitazone rescues dendrite loss and spatial memory of mutant FUS rats (Huang et al., 2012). While the effect of C9orf72 mutation on mitochondrial biogenesis is still clouded, recent studies showed that mutant C9orf72 enhances PGC-1 $\alpha$  expression in patient fibroblasts (Onesto et al., 2016) and interacts with the mitochondrial import translocase Tim50 in Neuro2A cells (Blokhuys et al., 2016).

### Mitochondrial dynamics in ALS

Studies on ALS patients and animal models have agreed that mitochondrial dynamics balance is altered in this pathology, leaning towards excessive fragmentation of mitochondria. Smaller mitochondria have been described in different models expressing ALS mutant SOD1 (Raimondi et al., 2006; Magrané et al., 2009, 2012; Vande Velde et al., 2011; Liu et al., 2013; Song et al., 2013; Finelli et al., 2015) and linked to a misexpression of mitochondrial dynamics genes. Indeed, studies on mouse spinal cord and skeletal muscles have shown that mutant SOD1 downregulates Mfns (Liu et al., 2013; Russell et al., 2013) as well as OPA1, while levels of phosphorylated DRP1 and Fis1 were particularly elevated (Liu et al., 2013). Interestingly, DRP1 inactivation recovers normal morphology of mitochondria and prevents death of mutant SOD1-expressing neurons (Song et al., 2013).

Studies realized on *in vitro* and *in vivo* TDP-43 models have shown a tendency of mitochondria towards fragmentation (Xu et al., 2010, 2011; Wang et al., 2013, 2016; Magrané et al., 2014; Finelli et al., 2015; Khalil et al., 2017). Few

groups sought to decipher the mechanisms behind the abnormal TDP-43-induced mitochondrial fission. For that purpose, we have measured expression levels of genes regulating mitochondrial dynamics. We have shown that expression of pro-fission factor DRP1 remains unchanged in *Drosophila* brains expressing TDP-43 (Khalil et al., 2017), while Xu et al. (2010) reported an increase in DRP1 phosphorylation in transgenic mice. On the other hand, we reported that TDP-43 does not modify the expression of fusogenic factor OPA1 in *Drosophila* neurons, while another group discovered in mutant TDP-43 mice that OPA1 expression increases after birth then decreases with time (Stribl et al., 2014). The use of either a mutant or a wild-type form of TDP-43 might justify this difference. More importantly, we and others agree that TDP-43 decreases the expression of the fusogenic factor Mfn in patient muscles (Russell et al., 2013), transgenic mice (Xu et al., 2010) and *Drosophila* neurons (Khalil et al., 2017) (**Figure 1**). TDP-43 downregulates *mfn* expression by binding directly to its mRNA (Khalil et al., 2017). Interestingly, *mfn* overexpression restores mitochondrial length, movement and function in TDP-43-expressing rat motor neurons (Wang et al., 2013) and ameliorates neuromuscular junction dysfunction and locomotor defects in TDP-43-expressing flies (Khalil et al., 2017). Hence, we propose that TDP-43 induces excessive mitochondrial division by holding up the fusion process between mitochondria.

Mitochondrial fragmentation has been reported in motor neurons expressing wild-type or mutant FUS as well as in fly models (Tradewell et al., 2012; Deng et al., 2015). Patient fibroblasts expressing ALS mutant C9orf72 also show shortened mitochondria (Onesto et al., 2016). Mutations in CHCHD10 which is enriched at mitochondrial cristae junctions have been linked to ALS (Bannwarth et al., 2014). Again, skin fibroblasts from patients with a CHCHD10 mutation exhibit reduced mitochondrial length (Bannwarth et al., 2014). Thus, unbalanced mitochondrial dynamics seems to be a common feature in ALS.

### Mitophagy in ALS

Mitophagy can be considered as the most affected MQC mechanism in ALS. Indeed, mutations in genes regulating the mitophagy process such as *VCP*, *optineurin* and *TBK1* are directly linked to ALS (for review, see Majcher, 2015). ALS mutant *VCP* is unable to migrate to damaged mitochondria and segregate ubiquitinated proteins, therefore causing abnormal mitochondrial accumulation in mouse embryonic fibroblasts and fly muscles (Kim et al., 2013; Kimura et al., 2013). Moreover, Moore and Holzbaur showed in HeLa cells that mutations in *optineurin* and *TBK1* interfere with LC3 recruitment to depolarized mitochondria, leading to reduced mitophagic rate (Moore and Holzbaur, 2016).

In other forms of ALS, mitophagy is also likely altered since accumulation of autophagic vacuoles colocalized with mitochondria have been reported in mutant SOD1 mouse motor neurons (Xie et al., 2015) and in patient fibroblasts expressing mutant C9orf72 (Onesto et al., 2016). Of interest, physical interaction between C9orf72 with the autophagy initiator ULK1 strongly suggests a role of C9orf72 in the autophagy process (Sullivan et al., 2016). However, how it regulates autophagy remains unclear.

Several studies on patient tissues and murine models in-

dicate that TDP-43 leads to abnormal aggregation of mitochondria, mainly in the perinuclear somatic space of motor neurons (Shan et al., 2010; Xu et al., 2010, 2011; Janssens et al., 2013; Wang et al., 2013; Magrané et al., 2014). Mitochondrial clusters have also been reported in transgenic rat cortical neurons expressing mutant FUS (Huang et al., 2012). Such perinuclear clusters of mitochondria are reminiscent of deficient mitochondria undergoing mitophagy. Accordingly, PINK1 and Parkin expression levels are increased in HEK293 cells overexpressing FUS, and downregulating either protein partially rescues the abnormal phenotype of *Drosophila* expressing FUS (Chen et al., 2016). However, contradictory data concerning the effect of TDP-43 on Parkin expression have been collected on A315T mutant TDP-43 mice (Hebron et al., 2013; Stribl et al., 2014). On the other hand, clusters of mitochondria in TDP-43 or FUS animal models may not be ubiquitinated (Shan et al., 2010; Cannon et al., 2012; Huang et al., 2012). In addition, whereas Hong et al. (2012) showed that TDP-43 increases the localization of autophagic marker LC3 on mitochondria in NSC-34 cells, recent evidence reported that LC3 is not even activated in the presence of TDP-43 (Zhang et al., 2010; Janssens et al., 2013; Onesto et al., 2016).

Another hypothesis would be that TDP-43 disrupts the anterograde transport of mitochondria, which could justify their accumulation in the neuronal soma as well as their absence in neuromuscular junctions (Shan et al., 2010). Since kinesin-associated proteins have been detected in TDP-43-positive cytoplasmic aggregates in mouse motor neurons (Shan et al., 2010), their sequestration might indicate a probable deregulation of mitochondrial axonal transport (**Figure 1**). It has also been reported that TDP-43 and FUS can prevent the interaction between vesicle-associated membrane protein-associated protein B (VAPB) and protein tyrosine phosphatase interacting protein 51 (PTPIP51) in NSC-34 cells and mouse spinal cords, decreasing the ER-mitochondria contacts (Stoica et al., 2014, 2016) (**Figure 1**). This might interrupt the calcium flux between both organelles and cause mitochondria to stagnate in neuronal regions enriched in calcium. It is also worth mentioning that mutations in VAPB have been described in ALS, with mutant VAPB blocking the anterograde transport of mitochondria in rat cortical axons (Mórotz et al., 2012). Therefore, further works are required to definitely demonstrate that mitophagy is perturbed in TDP-43 and FUS models and possibly involved in ALS pathogenesis. If it is proven that mitophagy is the main altered MQC in ALS, then pharmacological agents should be more than ever designed to restore this process.

### Conclusion

In the last decade, major insights into the molecular basis of ALS have arisen from the identification of new ALS-linked genes. In view of the huge number of genes, one major challenge is to unravel common pathways in ALS. This is particularly critical to develop therapeutic targets with a large spectrum. MQC is emerging as a key common pathway directly or secondarily impaired by ALS causing genes, but also in other neurodegenerative diseases such as Parkinson's disease. Indeed, these pathologies share common mitochondrial alterations while affecting distinct neuronal populations. This

includes excessive mitochondrial fission and perturbed mitophagy, as well as reduced complex I expression and activity which have been reported in familial and sporadic forms of Parkinson's disease (for review, see Hu and Wang, 2016) and lately in ALS by Wang et al. (2016). In such a condition, neurons may quickly reach a saturation state of defective mitochondria. Nevertheless, this raises an important question: how alterations of MQC result in selective motor neuronal damage in ALS while dopaminergic neurons are more vulnerable in Parkinson's disease? Additional investigations are needed in the upcoming years to answer this challenging question and deepen our understanding of ALS pathogenesis.

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**Additional file:** Additional Table 1 Mitochondrial quality control processes that are altered by ALS causing genes

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**Additional Table 1 Mitochondrial quality control processes that are altered by ALS causing genes**

ALS-related gene	Gene function	Studied gene form	Study model	Mitochondrial quality control defects	Reference
SOD1	Anti-oxidative defense	G93A	Mice motor neurons	Activated mitophagy: degenerating mitochondria	Kong and Xu, 1998
		G93A	NSC-34 cells	Impaired MPQC: decreased Lon and Hsp70 expression	Fukada et al., 2004
		G93A	NSC-34 cells	Mitochondrial fragmentation	Raimondi et al., 2006
		G93A	Mice motor neurons	Impaired anterograde mitochondrial transport	De Vos et al., 2007
		G93A	Mice spinal cord, neuroblastoma cells	Increased Hsp70 expression	Yamashita et al., 2007
		G93A	NSC-34 cells	Mitochondrial fragmentation	Magrané et al., 2009
		G37R, G85R	Mice motor neurons	Mitochondrial fragmentation	Vande Velde et al., 2011
		G93A	Rat cortical and motor neurons	-Mitochondrial fragmentation only in motor neurons -Impaired mitochondrial transport only in motor neurons	Magrané et al., 2012
		G93A	Mice spinal cord and muscles	Impaired mitochondrial biogenesis: decreased expression of PGC-1 $\alpha$ and downstream factors	Thau et al., 2012
		G93A	Mice anterior half of lumbar spinal	Mitochondrial fragmentation: increased P-DRP1 and Fis1 levels versus decreased Mfn1 and OPA1 levels	Liu et al., 2013
		G93A	Mice skeletal muscles	-Impaired mitochondrial biogenesis: decreased PGC-1 $\alpha$ , PGC-1 $\beta$ and NRF1 levels -Mitochondrial fragmentation: decreased Mfn1/2 levels	Russell et al., 2013
		G93A	Rat motor neurons	-Mitochondrial fragmentation -Impaired mitochondrial transport	Song et al., 2013
		G93A	Mice motor and sciatic nerves	-Mitochondrial fragmentation only in sciatic nerves -Impaired mitochondrial transport only in sciatic nerve	Magrané et al., 2014
		G93A	Mice motor neurons	Activated mitophagy: accumulation of mitochondria-containing autophagic vacuoles	Xie et al., 2015
		G93A	Mice brain stem, spinal cord and peripheral tissues	Impaired mitochondrial biogenesis: decreased PGC-1 $\alpha$ levels only in the nervous system	Bayer et al., 2017
TDP-43	RNA metabolism	WT, CTF	M17 human neuroblastoma cells	Mitophagy not activated: no conversion of LC3-I to LC3-II	Zhang et al., 2010
		WT, CTF	Fly photoreceptor neurons	Activated mitophagy: degenerating mitochondria and autophagic vacuoles only with WT TDP-43	Li et al., 2010
		WT	Mice brain neurons	Mitochondrial fragmentation: increased P-DRP1 and Fis1 levels versus decreased Mfn1 levels	Xu et al., 2010
		WT, M337V	Mice brain neurons	No mitochondrial fragmentation: Fis1 and Mfn1 levels unchanged	Xu et al., 2011
		WT, CTF, Q331K, M337V	NSC-34 cells	Activated mitophagy: increased LC3-II and decreased p62 on mitochondria	Hong et al., 2012
		WT, Q331K, M337V	Rat and mice motor neurons	-Mitochondrial fragmentation -Impaired mitochondrial transport	Wang et al., 2013
		WT, M337V	Mice brain neurons	Mitophagy not activated: no significant change in LC3 and p62 levels	Janssens et al., 2013
		A315T	Mice motor and sciatic nerves	-Mitochondrial fragmentation only in sciatic nerves -Impaired mitochondrial transport only in sciatic nerves	Magrané et al., 2014
		A315T	Mice brain neurons	-Impaired mitophagy: decreased Parkin levels -Mitochondrial fragmentation: decreased OPA1 levels	Stribl et al., 2014
		M337V	NSC-34 cells	Mitochondrial fragmentation	Finelli et al., 2015
		M337V	NSC-34 cells	Mitochondrial fragmentation	Finelli et al., 2015
		A382T	Patient fibroblasts	Mitochondrial fragmentation: increased Fis1 levels, Mfn1 levels unchanged	Onesto et al., 2016
		A382T	Patient fibroblasts	Mitochondrial fragmentation: increased Fis1 levels, Mfn1 levels unchanged	Onesto et al., 2016

Table 1 Continued

ALS-related gene	Gene function	Studied gene form	Study model	Mitochondrial quality control defects	Reference
		A382T	Patient fibroblasts	Mitochondrial fragmentation: increased Fis1 levels, Mfn1 levels unchanged	Onesto et al., 2016
		WT, M337V	Fly motor neurons	Unaltered mitochondrial transport	Baldwin et al., 2016
		WT, G298S, A382T	HEK293 cells, rat primary neurons, patient fibroblasts	Mitochondrial fragmentation	Wang et al., 2016
		WT, A315T	Mice motor cortex	Mitochondrial fragmentation	Wang et al., 2016
		WT, G298S	Fly brain neurons	Mitochondrial fragmentation: decreased Mfn levels	Khalil et al., 2017
FUS	RNA metabolism	WT, R521G, R521H	Mice motor neurons	Mitochondrial fragmentation only with FUS mutants	Tradewell et al., 2012
		WT, P525L	HT22 cells, mice and fly cortical neurons	Mitochondrial fragmentation	Deng et al., 2015
		WT, P525L	HEK293 cells	Activated mitophagy: increased PINK1, Parkin and Ub-Miro1 levels	Chen et al., 2016
		WT, P525L	Fly motor neurons	Impaired mitochondrial transport	Chen et al., 2016
C9orf72	Nucleocytoplasmic and endosomal trafficking, autophagy	GGGGCC mutant	Patient fibroblasts	-Mitochondrial fragmentation -Altered mitophagy: degenerating mitochondria and autophagic vacuoles, but LC3-I not converted to LC3-II -Impaired mitochondrial biogenesis: increased PGC-1 $\alpha$ levels	Onesto et al., 2016
VCP	Protein quality control, vesicle trafficking	A232E	MEFs	Reduced mitophagy	Kim et al., 2013
OPTN		E478G	HeLa cells	Reduced mitophagy: decreased LC3 recruitment to mitochondria	Wong and Holzbaur, 2014
	Autophagy, vesicle trafficking	E478G, Q398X	HeLa cells	Reduced mitophagy: decreased LC3 recruitment to mitochondria	Moore and Holzbaur, 2016
TBK1	Autophagy	E696K	HeLa cells	Reduced mitophagy: decreased LC3 recruitment to mitochondria	Moore and Holzbaur, 2016
CHCHD10	Mitochondrial cristae uncton and nucleoid regulation	S59L	Patient fibroblasts	Mitochondrial fragmentation	Bannwarth et al., 2014
VAPB	Vesicle trafficking, calcium signaling	WT, P56S	Rat cortical neurons	Reduced anterograde mitochondrial transport only with mutant VAPB	Morotz et al., 2012

ALS: Amyotrophic lateral sclerosis; CTF: C-terminal fragments; LC3: microtubule-associated protein 1A/1B-light chain 3; MEFs: murine embryonic fibroblasts; MPQC: mitochondrial protein quality control; P: phosphorylated; Ub, ubiquitinated; VAPB: vesicle-associated membrane protein-associated protein B/C; VCP: valosin-containing protein; WT: wild-type.